DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

December 23,2014

FUJIREBIO DIAGNOSTICS, INC.
STACEY DOLAN
MANAGER, REGULATORY AFFAIRS
201 GREAT VALLEY PKWY.
MALVERN PA 19355-1307

Re: K140436
Trade/Device Name: ARCHITECT Galectin-3 Reagent Kit
ARCHITECT Galectin-3 Calibrators
ARCHITECT Galectin-3 Controls
Regulation Number: 21 CFR 862.1117
Regulation Name: B-type natriuretic peptide test system
Regulatory Class: II
Product Code: OSX, JIT, JJX
Dated: November 12, 2014
Received: November 13, 2014

Dear Ms. Stacey Dolan:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the

electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Katherine Serrano -S

For: Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
k140436

Device Name
ARCHITECT Galectin-3

Indications for Use *(Describe)*
Reagent Kit:

The ARCHITECT Galectin-3 assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of galectin-3 in human serum and EDTA plasma.

The ARCHITECT Galectin-3 assay may be used in conjunction with clinical evaluation as an aid in assessing the prognosis of patients diagnosed with chronic heart failure (HF). The ARCHITECT Galectin-3 assay is used with the ARCHITECT i System with STAT protocol capability.

Calibrators:

The ARCHITECT Galectin-3 Calibrators are for the calibration of the ARCHITECT i System when used for the quantitative determination of galectin-3 in human serum and EDTA plasma.

Controls:

The ARCHITECT Galectin-3 Controls are for the verification of the accuracy and precision of the ARCHITECT i System when used for the quantitative determination of galectin-3 in human serum and EDTA plasma.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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Section 5 510(k) SUMMARY

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of 21 CFR 807.92.

A. 510(k) Number:

k140436

B. Purpose for Submission:

New device

C. Measurand:

Galectin-3

D. Type of Test:

Quantitative, Automated chemiluminescence immunoassay on the ARCHITECT *i* Systems

E. Applicant:

Address: Fujirebio Diagnostics, Inc.
201 Great Valley Parkway
Malvern, PA 19355

Contact person: Stacey Dolan
(610) 240-3843
dolans@fdi.com

Summary preparation date**:** November 12, 2014

F. Proprietary and Established Names:

ARCHITECT Galectin-3 Reagent Kit
ARCHITECT Galectin-3 Calibrators
ARCHITECT Galectin-3 Controls

G. Regulatory Information:

1. Regulation section:
   21 CFR § 862.1117, Test, Natriuretic Peptide
   21 CFR § 862.1150, Calibrator
   21 CFR § 862.1660, Quality Control Material (Assayed and Unassayed)

2. Classification:
   Class II

3. Product code:
   OSX, Galectin-3 In Vitro Diagnostic Assay

JIT, Calibrator, Secondary
JJX, Single (Specified) Analyte Controls (Assayed and Unassayed)

4. Panel:
   75, Chemistry

H. Intended Use:

1. Intended use(s):
   See indications for use below.

2. Indication(s) for use:

   Reagent Kit
   The ARCHITECT Galectin-3 assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of galectin-3 in human serum and EDTA plasma.
   The ARCHITECT Galectin-3 assay may be used in conjunction with clinical evaluation as an aid in assessing the prognosis of patients diagnosed with chronic heart failure (HF). The ARCHITECT Galectin-3 assay is used with the ARCHITECT *i* System with *STAT* protocol capability.

   Calibrators
   The ARCHITECT Galectin-3 Calibrators are for the calibration of the ARCHITECT *i* System when used for the quantitative determination of galectin-3 antigen in human serum and EDTA plasma.

   Controls
   The ARCHITECT Galectin-3 Controls are for the verification of the accuracy and precision of the ARCHITECT *i* System when used for the quantitative determination of galectin-3 in human serum and EDTA plasma.

3. Special conditions for use statement(s):
   Prescription use only

4. Special instrument requirements:
   Abbott ARCHITECT *i* 2000 SR System analyzers in STAT mode

I. Device Description:

The ARCHITECT Galectin-3 assay is a two-step immunoassay for the quantitative determination of galectin-3 in human serum or EDTA plasma using CMIA technology with flexible assay protocols, referred to as Chemiflex.

In the first step, sample and M3/38 anti-galectin-3 coated paramagnetic microparticles are combined. Galectin-3 present in the sample binds to the anti-galecin-3 coated microparticles. After washing, 87B5 anti-galectin-3 acridinium-labeled conjugate is added to create a reaction mixture in the second step. Following another wash cycle, pre-trigger and trigger solutions are added to the reaction mixture. The resulting chemiluminescent reaction is measured as relative light units (RLUs).

A direct relationship exists between the amount of galectin-3 in the sample and the RLUs detected by the ARCHITECT *i* System optics. The kit is composed of the following:

ARCHITECT Galectin-3 Reagent Kit (5P03)
The ARCHITECT Galectin-3 Reagent Kit consists of 100 (1 × 100) tests. Each kit contains paramagnetic microparticles coated with the anti-galectin-3 Rat monoclonal antibody M3/38, and an acridinium-labeled anti-galectin-3 mouse monoclonal antibody 87B5 conjugate. Reagents can be stored on-board the ARCHITECT *i* System in accordance with assay-specific instructions.

MICROPARTICLES 1 Bottle (6.6 mL) Anti-galectin-3 (rat, monoclonal) coated microparticles in PBS buffer with protein (bovine) stabilizers. Minimum concentration: 0.08% solids. Preservative: ProClin 300.
CONJUGATE 1 Bottle (5.9 mL) Anti-galectin-3 (mouse, monoclonal) acridinium-labeled conjugate in PBS buffer with protein (bovine) stabilizers. Minimum concentration: 800 ng/mL. Preservative: ProClin 300.

ARCHITECT Galectin-3 Calibrators (5P03-01)
The ARCHITECT Galectin-3 Calibrators are used for the calibration of the ARCHITECT *i* System. Each calibrator kit contains one bottle each of Calibrators A, B, C, D, E, and F. The calibrator kit is packaged separately.

CALIBRATORS 6 Bottles (4.0 mL each) of ARCHITECT Galectin-3 Calibrators. Calibrators A through F are prepared with artificial matrix. Calibrators B through F contain recombinant human galectin-3. Preservatives: EDTA and ProClin 950.

The calibrators are at the following concentrations:

Calibrator	Concentration (ng/mL)
CAL A	0.0
CAL B	5.7
CAL C	11.4
CAL D	22.8
CAL E	68.4
CAL F	114.0

ARCHITECT Galectin-3 Controls (5P03-10)
The ARCHITECT Galectin-3 Controls are used for the verification of the accuracy and precision of the ARCHITECT *i* System. Each control kit contains one bottle each of low, medium, and high control. The control kit is packaged separately.

CONTROLS 3 Bottles (8.0 mL each) of ARCHITECT Galectin-3 Controls. The Low, Medium, and High Controls are prepared with artificial matrix and contain recombinant human galectin-3. Preservatives: EDTA and ProClin 950.

The calibrators are at the following concentrations:

Control	Concentration Target (ng/mL)	Concentration Range (ng/mL)
Low Control	9.1	6.4 – 11.8
Medium Control	20.5	14.4 – 26.7
High Control	74.1	51.9 – 96.3

Other Materials/Equipment Required (not Provided):

- MULTI-ASSAY MANUAL DILUENT 1 Bottle (100 mL) ARCHITECT *i* Multi-Assay Manual Diluent containing phosphate buffered saline solution. Preservative: antimicrobial agent.
- PRE-TRIGGER SOLUTION Pre-Trigger Solution containing 1.32 % (w/v) hydrogen peroxide.
- TRIGGER SOLUTION Trigger Solution containing 0.35N sodium hydroxide.
- WASH BUFFER Wash Buffer containing phosphate buffered saline solution. Preservative: Antimicrobial Agents.
- ARCHITECT *i*2000*SR* System in STAT mode
- ARCHITECT *i* System ASSAY CD-ROM – US – Addition A (3K50)
- ARCHITECT i System e-Assay CD-ROM at www.abbottdiagnostics.com
- ARCHITECT *i* REACTION VESSELS
- ARCHITECT *i* SAMPLE CUPS
- ARCHITECT *i* SEPTUM
- ARCHITECT *i* REPLACEMENT CAPS
- Pipettes / Pipette Tips

J. Substantial Equivalence Information:

1. Predicate device name(s):
   BG Medicine, Inc. Galectin-3 Assay

2. Predicate 510(k) number(s):
   k093758

3. Comparison with predicate:

Similarities		
	ARCHITECT Galectin-3 (Proposed Device)	**BG Medicine Galectin-3 Assay (Predicate Device) k093758**
Device Type	*In vitro* diagnostic	*In vitro* diagnostic
Classification	Class II	Class II
CFR section	862.117	862.117
Product Code	OSX	OSX
Product Usage	Clinical and Hospital laboratories	Clinical and Hospital laboratories
Intended Use	Quantitative determination of galectin-3 in human serum and EDTA plasma. ARCHITECT Galectin-3 assay may be used in conjunction with clinical evaluation as an aid in assessing the prognosis of patients diagnosed with chronic heart failure (HF).	Quantitatively measures galectin-3 in serum or EDTA plasma by enzyme-linked immunosorbent assay (ELISA) on a microtiter plate platform, to be used in conjunction with clinical evaluation as an aid in assessing the prognosis of patients diagnosed with chronic heart failure (HF).
Assay Range	5.5 – 103.1 ng/mL	1.4 – 94.8 ng/mL
Type of Specimen	Human Serum or EDTA plasma	Human Serum or EDTA plasma
Specimen Collection Method	Routine Phlebotomy Techniques	Routine Phlebotomy Techniques
Capture Antibody	Mouse monoclonal (M3/38)	Mouse monoclonal (M3/38)
Detection Antibody	Mouse monoclonal (87B5)	Mouse monoclonal (87B5)
Analyte	Human galectin-3	Human galectin-3

Differences		
	ARCHITECT Galectin-3 (Proposed Device)	**BG Medicine Galectin- 3 Assay (Predicate Device) k093758**
Instrument System	ARCHITECT *i* System	None
Principle of Operation	Chemiluminscent Microparticle Immunoassay (CMIA)	Manual Enzyme Linked Immunosorbent Assay (ELISA)
Calibrators	6 Levels (0.0 – 114.0 ng/mL) Ready to Use -Liquid -Supplied as separate kit	1 Level (12 ng/vial) Serial diluted prior to use -Lyophilized -Supplied with Kit
Controls	-3 Levels (9.1, 20.5, and 74.1 ng/mL) -Liquid -Supplied as separate kit	-2 Levels (18.4 and 69 ng/mL) -Lyophilized -Supplied with Kit
Interpretation of Results	Calibrator Curve	Standard Curve
Cut-off	galectin-3 risk categories: • galectin-3 greater than 17.8 ng/mL •galectin-3 less than or equal to 17.8 ng/mL	galectin-3 risk categories: • galectin-3 greater than 25.9 ng/mL • galectin-3 between 17.8 and 25.9 ng/mL •galectin-3 less than or equal to 17.8 ng/mL

K. Standard/Guidance Document Referenced (if applicable):

- CLSI C28-A3c: Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline
- CLSI EP6-A: Evaluation of Linearity of Quantitative Measurement Procedures, A Statistical Approach: Approved Guideline
- CLSI EP07-A2: Interference Testing in Clinical Chemistry; Approved Guideline
- CLSI EP14-A2: Evaluation of Matrix Effects; Approved Guideline
- CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline
- CLSI EP05-A2: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline
- CEN13640: Stability Testing of In Vitro Diagnostic Reagents
- Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable - Guidance for Sponsors, Institutional Review Boards, Clinical Investigators and FDA Staff
- Class II Special Control Guidance Document for B-Type Natriuretic Peptide Premarket Notifications; Final Guidance for Industry and FDA Reviewers. Document issued on: November 30, 2000

L. Test Principle

The ARCHITECT Galectin-3 assay is a two-step immunoassay for the quantitative determination of galectin-3 in human serum or EDTA plasma using CMIA technology with flexible assay protocols, referred to as Chemiflex. In the first step, sample and M3/38 anti-galectin-3 coated paramagnetic microparticles are combined. Galectin-3 present in the sample binds to the anti-galecin-3 coated microparticles. After washing, 87B5 anti-galectin-3 acridinium-labeled conjugate is added to create a reaction mixture in the second step. Following another wash cycle, pre-trigger and trigger solutions are added to the reaction mixture. The resulting chemiluminescent reaction is measured as relative light units (RLUs). A direct relationship exists between the amount of galectin-3 in the sample and the RLUs detected by the ARCHITECT *i* System optics.

The ARCHITECT Galectin-3 Calibrators are for the calibration of the ARCHITECT *i* System when used for the quantitative determination of galectin-3 antigen in human serum and EDTA plasma.

The ARCHITECT Galectin-3 Controls are for the verification of the accuracy and precision of the ARCHITECT *i* System when used for the quantitative determination of galectin-3 in human serum and EDTA plasma.

M. Performance Characteristics (if/when applicable):

Data were generated using the ARCHITECT *i* 2000SR System with the *STAT* protocol.

1. Analytical performance:

   a. *Precision/Reproducibility:*

Precision

The ARCHITECT Galectin-3 assay is designed to have an imprecision of ≤ 10% Total CV for samples with galectin-3 concentrations ranging from 4.0 to 114.0 ng/mL.

A study was performed based on guidance from the National Committee for Clinical Laboratory Standards (NCCLS) document EP5-A2. Testing was conducted using one (1) lot of ARCHITECT Galectin-3 Reagents, Calibrators, and Controls, and one (1) ARCHITECT *i* 2000_{SR} instrument. Three (3) levels of controls and five (5) levels of human serum and plasma panels were assayed with a minimum of two (2) replicates at two (2) separate times per day for twenty (20) different days. A single calibration curve was used throughout the study.

The precision analyses determined that the total precision for one (1) lot individually is ≤ 5.8% for all samples in this study.

System Reproducibility

A study was performed based on guidance from the NCCLS document EP5-A2. Testing was conducted using two (2) lots of ARCHITECT Galectin-3 Reagents, Calibrators, and Controls on

two (2) different ARCHITECT *i* 2000SR instruments. Each reagent lot was matched with a different lot of calibrators and controls. Three (3) levels of controls and five (5) levels of human serum and plasma panels were assayed with a minimum of two (2) replicates at two (2) separate times per day for ten (10) different days for a total of forty (40) replicates for each lot. Each reagent lot used a single calibration curve throughout the study.

The precision analyses determined that the total reproducibility for two (2) lots is ≤ 4.7% for all samples in this study.

b. Linearity/assay reportable range:

A study was performed based on guidance from the CLSI document EP6-A. Two (2) serum samples (one low and one high for galectin-3 levels) and two (2) plasma samples (one low and one high for galectin-3 levels) were used for this study.

The high serum and high plasma samples were diluted with their respective low sample. The neat and diluted panels were tested in replicates of three (3) using the ARCHITECT Galectin-3 assay on the ARCHITECT *i*2000*SR* System in STAT mode.

Based on a +/-10% deviation from linearity (%DL), the data supports a linear range of 5.5 to 103.1 ng/mL for the ARCHITECT Galectin-3 assay.

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

The ARCHITECT Galectin-3 Calibrators are for the calibration of the ARCHITECT *i* System when used for the quantitative determination of galectin-3 antigen in human serum and EDTA plasma. 6 Bottles (4.0 mL each) are supplied for the ARCHITECT Galectin-3 Calibrators. Calibrators A through F are prepared with artificial matrix. Calibrators B through F contain recombinant human galectin-3. Preservatives: EDTA and ProClin 950. The calibrators are at the following concentrations:

Calibrator	Concentration (ng/mL)
CAL A	0.0
CAL B	5.7
CAL C	11.4
CAL D	22.8
CAL E	68.4
CAL F	114.0

There is currently no known internationally recognized consensus reference method or reference material for standardization. Galectin-3 assay values are expressed as ng/mL. This value is related to a Fujirebio Diagnostics maintained reference preparation. The primary calibrators for the ARCHITECT Galectin-3 assay were manufactured gravimetrically and produced based on protein content.

The stability data supports the current shelf life assignment for the ARCHITECT Galectin-3 Calibrators of 12 months.

The ARCHITECT Galectin-3 Controls are for the verification of the accuracy and precision of the ARCHITECT *i* System when used for the quantitative determination of galectin-3 in human serum and EDTA plasma. 3 Bottles (8.0 mL each) are supplied for the ARCHITECT Galectin-3 Controls. The Low, Medium, and High Controls are prepared with artificial matrix and contain recombinant human galectin-3. Preservatives: EDTA and ProClin 950. The controls are at the following concentrations:

Control	Concentration Target (ng/mL)	Concentration Range (ng/mL)
Low Control	9.1	6.4 – 11.8
Medium Control	20.5	14.4 – 26.7
High Control	74.1	51.9 – 96.3

The stability data supports the current shelf life assignment for the ARCHITECT Galectin-3 Controls of 12 months.

d. Detection limit:

The ARCHITECT Galectin-3 assay is designed to have a Limit of Quantitation (LoQ) of ≤ 4.0 ng/mL. Based on guidance from the CLSI document EP17-A2, a study was performed by diluting 7 normal human serum samples in ARCHITECT Galectin-3 Calibrator A. Two (2) lots of ARCHITECT Galectin-3 Calibrator A (run as the zero-level panel) and Low Level Panel Set were run in replicates of five (5), twice per day over three (3) days on two (2) ARCHITECT *i*2000SR Systems in STAT mode with two (2) ARCHITECT Galectin-3 assay reagent lots (N= 5x2x3x2x2 = 120).

The Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) determined for the ARCHITECT Galectin-3 assay was 1.0 ng/mL, 1.1 ng/mL, and 2.8 ng/mL respectively.

The LoQ met the predetermined acceptance criteria of LoD ≤ 4.0 ng/mL. These data support the performance claims of the assay.

e. Analytical specificity:

A study was conducted to evaluate the potential interference from other recombinant human galectin and collagen proteins in the ARCHITECT Galectin-3 assay.

Four (4) serum and four (4) patient plasma samples were used for this study. Three (3) serum samples and two (2) plasma samples were augmented with human galectin-3 antigen targeting a 'normal' concentration of galectin-3 (10-13 ng/mL) and an elevated concentration of galectin-3 (≈26 ng/mL). The other 3 samples (One (1) serum and two (2) plasma) were at the target concentrations and did not require augmentation. The eight (8) samples were supplemented with the various cross reactants each prepared at a concentration of 10 µg/mL in PBS.

The prepared samples were tested in replicates of three (3) using the ARCHITECT Galectin-3 assay on the ARCHITECT *i*2000*SR* System in STAT mode.

All individual patient samples supplemented with the various human recombinant galectin and collagen proteins resulted in a percent cross reactivity with the ARCHITECT Galectin-3 assay of ≤ 0.3% and support the performance claims of the assay (below 0.5%).

A study was performed based on guidance from the CLSI document EP07-A2. Potentially interfering drugs were evaluated to determine whether galectin-3 concentrations were affected when using the ARCHITECT Galectin-3 assay.

Serum and plasma samples selected based on their endogenous galectin-3 values which fell within or near the galectin-3 target ranges were used in this study. The predetermined galectin-3 targets were a 'normal' concentration of galectin-3 (10-13 ng/mL) and an elevated concentration near the upper end of the reference range for galectin-3 (≈26 ng/mL).

Each galectin-3 sample pool was split into 2 equal aliquots for each therapeutic tested. One aliquot was spiked with the therapeutic agent stock for use as the test sample. The samples were not diluted more than 5% by the agent. The other aliquot (control) was spiked with an equal volume of the same solvent used for therapeutic agent preparation for each respective therapeutic agent.

The data are summarized in the following table.

Therapeutic	Therapeutic Concentration	Percent Difference (%)
Acetaminophen (4-Acetamidophenol)	1324 µmol/L	-2.9%
Acetylsalicylic Acid	3.62 mmol/L	-0.7%
Amlodipine besylate	10.6 µmol/L	-0.1%
Ampicillin	152 µmol/L	-0.1%
L-Ascorbic Acid	342 µmol/L	1.9%
Atenolol	37.6 µmol/L	-0.4%
Caffeine	308 µmol/L	0.7%
Carvedilol	74 µmol/L	2.4%
Captopril	23 µmol/L	-1.9%
Chloramphenicol	155 µmol/L	1.1%
Diclofenac sodium salt	169 µmol/L	-0.7%
Digoxin	7.8 nmol/L	0.8%
(+)-cis-Diltiazem hydrochloride	576.5 µmol/L	-0.5%
Disopyramide	29.5 µmol/L	-2.5%
Dopamine hydrochloride	5.87 µmol/L	4.0%
Enalaprilat dihydrate	0.86 µmol/L	1.6%
Furosemide	181 µmol/L	1.0%
Hydrochlorothiazide	20.2 µmol/L	0.0%
Ibuprofen	2425 µmol/L	-0.6%
Indomethacin	100 µmol/L	-1.7%
Lidocaine	51.2 µmol/L	0.1%
Lisinopril • $2H_2O$	0.74 µmol/L	-0.9%
Losartan potassium	130 µmol/L	-1.1%
Lovastatin (Simvastatin)	191 µmol/L	1.7%
Methyldopa	71 µmol/L	-2.3%
(±)-Metoprolol (+)-tartrate salt	18.7 µmol/L	-2.8%
Naproxen	2170 µmol/L	-1.0%
Nifedipine	1156 nmol/L	0.4%
Quinidine	37 µmol/L	-0.7%
Ramipril	14.4 µmol/L	0.0%
Spironolactone	1.44 µmol/L	-2.0%
Theophylline	222 µmol/L	-2.9%
Verapamil hydrochloride	244 µmol/L	0.6%
Warfarin	32.5 µmol/L	-2.1%
Trasylol/Aprotinin	100 KIE/mL	0.9%

A study was performed based on guidance from the Clinical and Laboratory Standards Institute (CLSI) document EP07-A2. Potentially interfering substances were evaluated to determine whether galectin-3 concentrations were affected when using the ARCHITECT Galectin-3 assay.

Serum and plasma samples selected based on their endogenous galectin-3 values which fell within or near the galectin-3 target ranges were used in this study. The predetermined galectin-3 targets were a 'normal' concentration of galectin-3 (10-13 ng/mL) and an elevated concentration near the upper end of the reference range for galectin-3 (≈26 ng/mL).

Each galectin-3 sample was split into two (2) aliquots for each endogenous substance tested. One (1) aliquot was spiked with an endogenous substance for use as the test sample. One (1) aliquot was spiked with an equal volume of ARCHITECT PBS (phosphate-buffered solution) for use as a control sample. The samples were not diluted more than 20% by the agent.

The data are summarized in the following table.

Potentially Interfering Substance	Interferent Concentration	Mean % Difference
Bilirubin (Unconjugated)	≥ 40 mg/dL	-3.8
Bilirubin (Conjugated)	≥ 40 mg/dL	0.7
Hemoglobin	≥ 250 mg/dL	4.6
Triglycerides	≥ 3000 mg/dL	4.4
Human Serum Albumin	≥ 12 g/dL	-4.7
Human Gamma Globulin	≥ 5 g/dL	-3.2
Cholesterol	≥ 500 mg/dL	3.7
Whole Blood Lysate b	5 mg/dL	4.7
Creatinine	≥ 5 mg/dL	0.5
Rheumatoid Factor	800 IU/mL	3.5
Human Anti-Mouse Antibodies	≥1000 ng/mL	1.1

f. Assay cut-off:

See Clinical Cutoff in M (4) below

2. Comparison studies:
   N/A

3. Clinical studies:

a. Clinical sensitivity:

See 3(c) below

b. Clinical specificity:

See 3(c) below

c. Other clinical supportive data (when a. and b. are not applicable):

The clinical performance of the ARCHITECT Galectin-3 assay was evaluated in a clinical validation study with specimens from a multicenter cohort of outpatients with chronic heart failure (HF). A total of 405 serum specimens were obtained at time of study entry from patients with varying degrees of chronic HF, encompassing all New York Heart Association (NYHA) classification categories. The median follow-up time for the study population was approximately 652 days.

Of the 405 baseline samples, 143 (35.3%) were obtained from females and 262 (64.7%) were obtained from males. The mean subject age was 58 years. The specimens were tested using the ARCHITECT Galectin-3 assay and categorized based on galectin-3 value as high risk (>17.8ng/mL) or low risk (≤17.8 ng/mL). A total of 226 subjects were in the high risk category and the remaining 179 subjects were in the low risk category. A multivariable Cox proportional hazards regression model was used to evaluate the association of galectin-3 category with the primary endpoint of hospitalization due to worsening HF, ventricular assist device placement, cardiac transplantation, or all-cause mortality.

The multivariable Cox proportional hazards regression model was adjusted for the parameters of age, gender, NYHA class, left ventricular ejection fraction (LVEF), diabetes status, and smoking status. The results of the regression model demonstrated a statistically significant higher risk for the occurrence of the primary endpoint in subjects with galectin-3 levels in the high risk category (> 17.8 ng/mL), compared with galectin-3 levels in the low risk category (≤ 17.8 ng/mL).

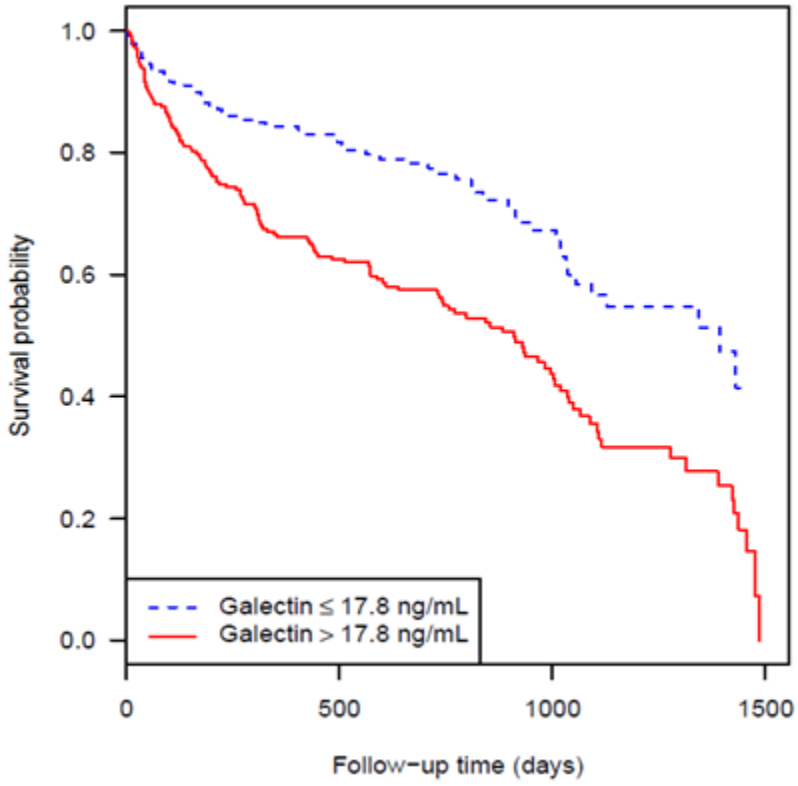
Hazard Ratio for Primary Endpoint (hospitalization due to worsening heart failure, ventricular assist device placement, cardiac transplantation, or all-cause mortality; first to occur) for Chronic Heart Failure Subjects

	Hazard Ratio[b] (95% Confidence Interval)
High Risk Category[a] (> 17.8 ng/mL)	1.753 (1.265 – 2.427)

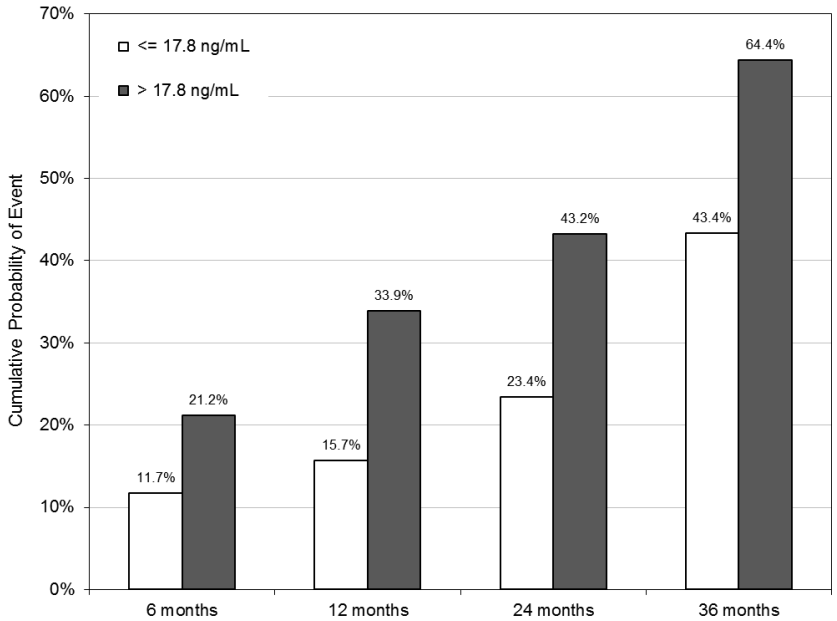
[a]adjusted for baseline risk factors: age, gender, NYHA functional classification, left ventricular ejection fraction, diabetes status, and smoking status.
[b] Hazard ratio is relative to the galectin-3 low risk category (≤ 17.8 ng/mL)

Elevated baseline levels of galectin-3 (>17.8 ng/mL) in chronic HF patients were shown to be significantly and independently associated with a higher risk of hospitalization due to worsening HF, ventricular assist device placement, cardiac transplantation, or all-cause mortality (first to occur).

The figure below presents the Kaplan-Meier Survival Function Estimates time-to-event (hospitalization due to worsening HF, ventricular assist device placement, cardiac transplantation, or all-cause mortality) based on the galectin-3 cutoff value of 17.8 ng/mL, where the probability of survival is plotted with the elapsed time in days from baseline (i.e., follow-up time).



The bar graph and table below depict the cumulative probability of the primary endpoint (hospitalization due to worsening HF, ventricular assist device placement, cardiac transplantation, or all-cause mortality) by galectin-3 category, at selected time points.



	Cumulative Probability (95% Confidence Interval) of Event for Primary Endpoint, by Galectin-3 Category, at Selected Time Points (in percent)			
Galectin-3 Category	**6 Months**	**12 Months**	**24 Months**	**36 Months**
≤ 17.8 ng/mL	11.7 (7.0 - 16.4)	15.7 (10.4 - 21.0)	23.4 (16.9 - 29.9)	43.4 (33.3 - 53.6)
> 17.8 ng/mL	21.2 (15.9 - 26.6)	33.9 (27.7 - 40.1)	43.2 (36.5 - 49.9)	64.4 (56.4 - 72.4)

Interpretation

ARCHITECT Galectin-3 assay results should be interpreted in conjunction with clinical evaluation as an aid in assessing the prognosis of patients diagnosed with chronic heart failure. In the clinical validation study, chronic heart failure patients with galectin-3 levels over 17.8 ng/mL were found to have a higher risk of adverse outcomes, defined as hospitalization for HF, placement of left ventricular assist device, cardiac transplantation and mortality, when compared to patients with levels below 17.8 ng/mL.

Interpretation Relative to Natriuretic Peptides

Galectin-3 and natriuretic peptides, such as NT-proBNP and BNP, are measures of separate and distinct biological processes. Galectin-3 and natriuretic peptides provide independent and complementary information on the prognosis of patients with chronic heart failure.
Elevated baseline levels of both galectin-3 and a natriuretic peptide have been associated with poorer prognosis in chronic heart failure patients, when compared to patients with low baseline levels of both markers. Elevated levels of one or the other marker, but not both, have been associated with a poorer prognosis in chronic heart failure when compared to patients with low levels of both markers, and with a better prognosis when compared to patients with elevated baseline levels of both markers.

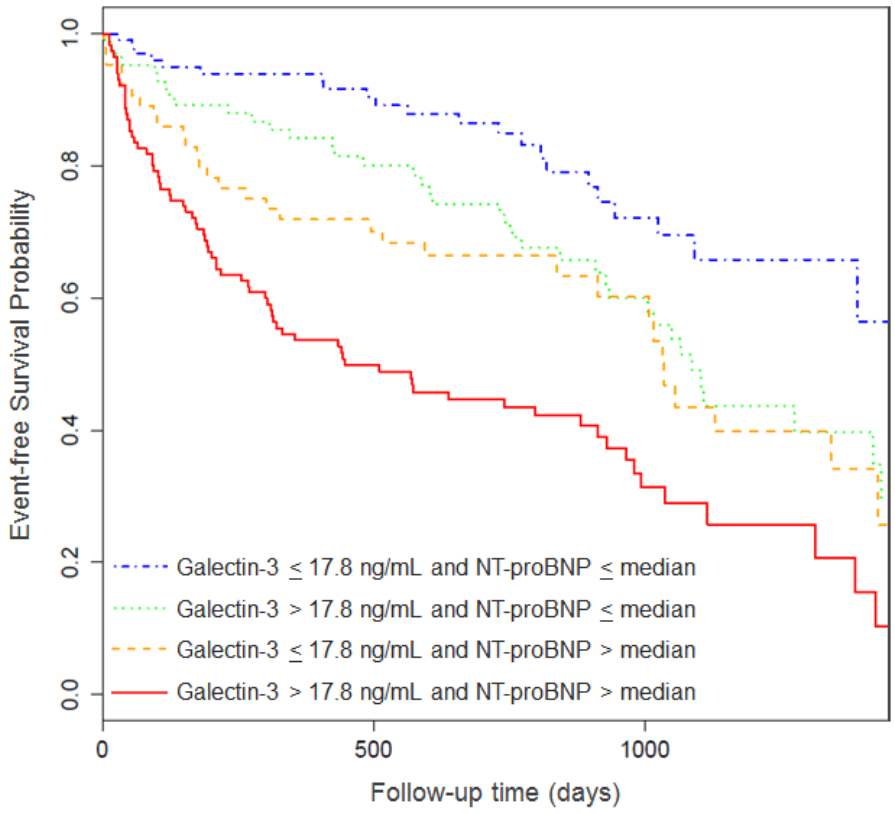
The table below illustrates this for N-terminal pro B-type natriuretic peptide (NT-proBNP) in the clinical validation study by evaluating primary endpoint event rates by categories of galectin-3 and NT-proBNP levels.

Event Rates by Joint Galectin-3 and NT-proBNP Category. Median NT-proBNP value in study is 1222 pg/mL.

	Subjects In Each Category Experiencing a Hospitalization for Heart Failure, Ventricular Assist Device Placement, Cardiac Transplantation, or Death		
	Within Overall Study	Hazard Ratio (95% Confidence Interval)	P-value
Galectin-3 ≤ 17.8 ng/mL and NT-proBNP ≤ median (N=99)	24.2%	1 (referent category)	NA
Galectin-3 ≤ 17.8 ng/mL and NT-proBNP > median (N=64)	48.4%	2.077 (1.216-3.549)	0.0075
Galectin-3 > 17.8 ng/mL and NT-proBNP ≤ median (N=83)	48.2%	1.835 (1.104-3.050)	0.0191
Galectin-3 > 17.8 ng/mL and NT-proBNP > median (N=115)	66.1%	4.014 (2.533-6.362)	<0.0001

The figure below is a plot of Kaplan-Meier survival function estimates by joint galectin-3/NT-proBNP categories, for the study endpoint.

Kaplan-Meier curves for the endpoint of the clinical validation study, by galectin-3 and NT-proBNP levels. Logrank test p-value <0.001



4. Clinical cut-off**:**

See 3(c) above

5. Expected values/Reference range:

An observational study was performed to determine the reference distribution for the ARCHITECT Galectin-3 assay. Galectin-3 levels were measured in 274 plasma samples from a population of apparently healthy subjects without known heart disease but that otherwise resemble the heart failure patient population by age and gender distribution.

Specimens were from women between the ages of 60 and 80 years (n = 133) and men between the ages of 55 and 80 (n = 141). The reference population consisted of the following race/ethnic groups:

- 55 African-American
- 189 Caucasian
- 12 Hispanic
- 9 Other
- 9 Asian

All subjects had detectable galectin-3 levels (minimum - maximum: 6.8 - 54.4 ng/mL) within the measuring interval of the ARCHITECT Galectin-3 assay. The 97.5% of the galectin-3 reference population was 27.5 ng/mL. The data are summarized in the following table.

Percentile (%)	Galectin-3 Reference Population (ng/mL)
2.5	8.2
5	9.3
25	12.4
50	14.8
75	18.5
90	22.4
95	25.7
97.5	27.5

6. Conclusion

The results of these analytical (nonclinical) and clinical studies demonstrate that the ARCHITECT Galectin-3 assay is substantially equivalent to the performance of the BG Medicine Galectin-3 assay.

N. Proposed Labeling:

The labeling satisfies the requirements of 21 CFR Part 809.10.